REMARKS

Claims 23-29, 32, 34, 36, 39 and 54-56 are pending. Claims 1-22, 30, 31, 33, 35, 37-38 and 40-45 have been cancelled in this Amendment or in prior Replies. Claims 46-53 have been withdrawn from consideration due to the Examiner's restriction requirement. These claims have been cancelled or withdrawn from consideration without prejudice to, or disclaimer of, the subject matter thereof. Applicant reserves the right to file continuation applications directed to the subject matter of any claim cancelled for any reason.

The present amendment to claim 23 and cancellation of claim 30 place the application in better condition for examination. It is submitted that no new matter has been introduced by the present amendment, and entry of the same is respectfully requested. By the amendment and cancellation, Applicant does not acquiesce to the propriety of any of the Examiner's prior rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

I. Rejection of Claim 30 Under 35 U.S.C. § 112 ¶ 2

The Examiner rejected claim 30 under 35 U.S.C. § 112, ¶ 2, as being indefinite for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. Office Action mailed 26 August 2004, page 2. Applicant respectfully traverses. Without acquiescing to the propriety of this rejection, and solely to expedite prosecution of the present application, Applicant has cancelled claim 30 in this Reply. Accordingly, this rejection is moot. Applicant respectfully request that the Examiner reconsider and withdraw the present rejection of claim 30 under 35 U.S.C. § 112, ¶2.

II. Rejection of Claims 23-29, 32, 34, 36, 39, and 54-56 Under 35 U.S.C. § 103(a) Over U.S. Patent No. 6,287,825

The Examiner rejected claims 23-29, 32, 34, 36, 39, and 54-56 as being unpatentable under 35 U.S.C. § 103(a) over U.S. Patent No. 6,287,825 issued to Weissman et al. ("*Weissman* '825"). *Id.* at 4. Applicant respectfully traverses.

To maintain a proper rejection under 35 U.S.C. § 103, the USPTO must meet four conditions to establish a *prima facie* case of obviousness. First, the USPTO must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed

composition or device or carry out the claimed process. Second, the USPTO must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the USPTO must show the suggestion, teaching, or motivation to combine the prior art references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

The Examiner alleged that claims 23-29, 32, 34, 36, 39, and 54-56 are obvious because *Weissman '825* contemplates "(a) digesting separately nucleic acids from a mixture of at least two nucleic acid populations with at least one restriction enzyme . . . (b) ligating an adaptor sequence to the restriction fragments . . .; (c) amplifying adaptor-ligated restriction fragments generated in step (b) and in step (b) using an adaptor-specific primer to produce amplification products having different ends in respect to each of the at least [two] nucleic acid populations . . .; (d) hybridizing the amplification products of step (c) from the different nucleic acid populations with each other to generate a mixture comprising homoduplexes and heteroduplexes . . .; (f) eliminating mismatched heteroduplexes by using mismatch repair enzymes . . .; and (g) identifying, isolating, or separating fully-matched heteroduplexes, thereby identifying, isolating or separating nucleic acid fragments that are identical between the at least two nucleic acid populations. . ." Office Action, pages 4-5 (citations omitted).

According to the Examiner, *Weissman '825* also contemplates that homoduplexes and heteroduplexes can be distinguished and eliminated using enzymes and that *Weissman '825* suggests eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended double-stranded DNA fragments. *Id.* at 6. Thus, according to the Examiner while *Weissman '825* does not specifically teach eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III), *Weissman '825* does suggest using an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III) for eliminating blunt ended homoduplexes from heteroduplexes having forked ends. *Id.* Therefore, according to the Examiner, it would have been obvious to one of ordinary skill in the art at the

time the invention was made to have used an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III), in order to have achieved the benefit of eliminating blunt ended homoduplexes from heteroduplexes having forked ends for use in genetic analysis. *Id.*

As the following explanation of *Weissman '825* and the claimed method of the present application will demonstrate, a rejection under 35 U.S.C. § 103 for the reasons stated above is not warranted or proper.

Quoting column 7, lines 3-22 of *Weissman '825*, the Examiner argued that this reference suggests that homoduplexes and heteroduplexes can be distinguished and eliminated by using enzymes that specifically digest blunt ended double-stranded DNA fragments. *Id.* at 5-6. However, *Weissman '825* does not teach or suggest this method. In the passage quoted by the Examiner, *Weissman '825* only states that "[s]equences in the adapters ... allow selective cutting of homohybrid or heterohybrid DNA with restriction endonucleases." *Weissman '825*, Col. 7, lines 9-11. Thus, in *Weissman '825* homohybrids and heterohybrids are distinguished based on sequences in the adapters that result in cutting by a restriction endonuclease. This method is to be contrasted with digestion by an *exo*nuclease based on a blunt versus forked end. Further, according to the disclosure of *Weissman '825*, the restriction endonuclease may only cut the heterohybrids and not lead to the elimination of blunt ended homohybrids. Even more, if the hybrids produced by the method described in *Weissman '825* were treated with an exonuclease (which is not taught by *Weissman '825*), such treatment could lead to the elimination of the *heterohybrids*. This elimination is the opposite result of the goal of the claimed method which eliminates blunt ended homoduplexes. Finally, the method suggested in *Weissman '825* leads to the formation of forked homohybrids and blunt ended heterohybrids. This is also the opposite result of the claimed method, and as a result, *Weissman '825* does not teach or suggest the particular species of blunt ended homoduplexes and forked end heteroduplexes that are described in the claimed method. The foregoing discussion of *Weissman '825* illustrates that this reference does not teach the discrimination between blunt ended homoduplexes and forked end heteroduplexes by digestion with an exonuclease that specifically digests blunt ended double-stranded DNA fragments as claimed in the present application.

The Examiner also asserted that in column 1, *Weissman '825* teaches that digestion by Exo III eliminates homoduplexes from heteroduplexes (step (e) of the claimed invention). OA,

6. Column 1 of *Weissman '825,* however, discusses a method described in Nelson et al., *Nature Genetics*, 1993, 4:11-18 ("the Nelson et al. reference"). *Weissman '825*'s discussion of the Nelson et al. reference indicates that nucleic populations in this method can be digested only with restriction enzymes that produce protruding 3'-ends because this kind of end provides protection against Exo III digestion which is used later in the process. *Weissman '825*, column 1, lines 23-26. Hence, both homohybrids and heterohybrids have protruding 3'-ends in this method. Because both homohybrids and heterohybrids have protruding 3'-ends in the Nelson method, the selective elimination of homohybrids based on the presence of blunt versus forked ends is not possible. Further, in the Nelson method as described in lines 36-51 of column 1 of *Weissman '825*, homoduplexes, which are either fully methylated or non-methylated, are cleaved by restriction endonucleases that are specific to GATC sites and sensible to methylation. Heteroduplexes having a mismatch are nicked by MutSLH. After these steps, all molecules are subjected to digestion by Exo III, which can initiate digestion at a nick, a blunt end or a recessed 3'-end. In this method then, Exo III digests *cut* homoduplexes and *nicked* heteroduplexes having a mismatch *in the same step.* This method should be contrasted to the presently claimed method of Exo III digestion of blunt ended homoduplexes followed by elimination of mismatched heteroduplexes by mismatch repair enzymes.

Based on the foregoing, it should be clear that *Weissman '825* does not teach or suggest that digestion by Exo III eliminates blunt ended homoduplexes from forked end heteroduplexes. Furthermore, there is no suggestion of selective digestion based on the ends of homoduplexes and heteroduplexes because as described in *Weissman '825*, these hybrids are digested due to previously made cuts or nicks created by a restriction enzyme or MutSLH.

In rejecting claim 23 of the present application, the Examiner stated that the order of performing steps (e) and (f) (eliminating blunt ended homoduplexes and mismatched heteroduplexes respectively) is not critical to the method of the claimed invention. OA, page 8. This is not true. Indeed, the order of performing steps (e) and (f) *is* critical. The presently claimed method specifically requires elimination of blunt ended homoduplexes before elimination of mismatched heteroduplexes. The selective elimination of homoduplexes from heteroduplexes is based on the presence of different ends. Again, *Weissman '825* shows digestion of *cut* homohybrids and *nicked* heterohybrids having a mismatch *in the same step* regardless of end configuration. *Weissman '825*, Col. 1, lines 48-51. Therefore, *Weissman '825*

does not teach or suggest the specific elimination of blunt ended homoduplexes before elimination of mismatched heteroduplexes as required by the claims of the present application.

The present invention, as defined in the claims, is based on the use of a specific type of enzyme, exonuclease, to specifically digest blunt ended double-stranded DNA fragments in order to discriminate homoduplexes (with blunt ends) from heteroduplexes (with forked ends). The property of exonuclease that allows it to specifically digest blunt ended double-stranded DNA fragments has never been used previously to discriminate between homoduplexes and heteroduplexes. In addition to the novelty just described, this method also may be distinguished from other methods used to discriminate homohybrids and heterohybrids, such as those shown in *Weissman '825* and the Nelson et al. reference because (1) no methylation is required, so there are less enzymatic steps involved, (2) there is no internal nicking of self-self DNA, and (3) *any* restriction enzyme may be used in the initial digestion step. These factors that clearly distinguish the presently claimed method render the present rejection of the claims of the current application under 35 U.S.C. § 103 inappropriate. Thus, Applicant respectfully submits that claims 23-29, 32, 34, 36, 39, 54-56 are patentable over *Weissman '825* and respectfully requests that the Examiner reconsider and withdraw the rejections of these claims under 35 U.S.C. § 103.

The Examiner also rejected claim 30 under 35 U.S.C. § 103(a) as unpatentable over *Weissman '825* in view of Green et al. (PNAS (1990) 87: 1213-1217). OA, page 11. Applicant respectfully traverses. Without acquiescing to the propriety of this rejection, and solely to expedite prosecution of the present application, Applicant has cancelled claim 30 in this Reply. Accordingly, this rejection is moot and therefore should be withdrawn.

III. Rejection of Claims 23-29 and 34-45 Under 35 U.S.C. § 102(e) Over U.S. Patent No. 6,150,112

The Examiner rejected claims 23-29 and 34-45 as being anticipated under 35 U.S.C. § 102(e) by U.S. Pat. No. 6,150,112 issued to Weissman et al. ("*Weisman '112*"). *Id.* at 8. Applicant respectfully traverses.

In order to support an anticipation rejection under 35 U.S.C. § 102(e), the Examiner must show that each and every element of the claimed invention is shown identically in a single reference. *In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990) citing *Diversitech Corp v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988). Further, the elements of the prior

art must be arranged as in the claims under review. *Id.* citing *Lindemann Maschinenfabrik v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 485 (Fed. Cir. 1984). Thus, the references the Examiner asserts as prior art must contain all of the elements contemplated by the present invention in the same order and arrangement as presently claimed. As explained below, *Weisman '112* does not contain each and every element of the claimed invention as they presently appear. Therefore, the invention as presently claimed is novel and inventive over the prior art of record and the present rejection should be reconsidered and withdrawn.

The Examiner argued that *Weisman '112* anticipates the claims of the present invention because it contemplates "(a) digesting separately nucleic acids from a mixture of at least two nucleic acid populations with at least one restriction enzyme ...; (b) ligating an adaptor sequence to the restriction fragments ...; (c) amplifying adaptor-ligated restriction fragments generated in step (b) and in step (b) using an adaptor-specific primer to produce amplification products having different ends in respect to each of the at least [two] nucleic acid populations ...; (d) hybridizing the amplification products of step (c) from the different nucleic acid populations with each other to generate a mixture comprising homoduplexes and heteroduplexes ...; ... (f) eliminating mismatched heteroduplexes by using mismatch repair enzymes ...; [and] (g) identifying, isolating, or separating fully-matched heteroduplexes, thereby identifying, isolating or separating nucleic acid fragments that are identical between the at least two nucleic acid populations." OA, pages 8-9 (citations omitted).

The Examiner also argued that through a discussion of the Nelson et al. reference, *Weisman '112* teaches that homoduplexes and heteroduplexes can be distinguished and eliminated using enzymes. *Id.* at 9. The Examiner further argued that *Weisman '112* also contemplates eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended double-stranded DNA fragments. *Id.* Thus, according to the Examiner, while *Weisman '112* does not specifically teach eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III), it does suggest using an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III) for eliminating blunt ended homoduplexes from heteroduplexes having forked ends. *Id.* at 9-10. Therefore, according to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention

was made to have used an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III), in order to have achieved the benefit of eliminating blunt ended homoduplexes from heteroduplexes having forked ends for use in genetic analysis. *Id.*

First, and as stated previously, to sustain a rejection under 35 U.S.C. § 102(e), the Examiner must show that each and every element of the claimed invention is shown identically in a single reference. *In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990) citing *Diversitech Corp v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988). As stated by the Examiner, *Weisman '112* "does not specifically exemplify eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III)." OA, page 9. Because *Weisman '112* does not identically show each and every element of the claimed invention, a rejection under 35 U.S.C. § 102(e) is not proper.

While *Weisman '112* does not teach eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III), the Examiner argued that Weissman, 112's suggestion of using an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III) for eliminating blunt ended homoduplexes from heteroduplexes having forked ends would have made it obvious to one of ordinary skill in the art at the time the invention was made to have used an enzyme that specifically digests blunt ended double-stranded DNA fragments (e.g., Exo III), in order to have achieved the benefit of eliminating blunt ended homoduplexes from heteroduplexes having forked ends for use in genetic analysis. *Id.* at 10. However, *Weisman '112* does not describe the elimination of blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt ended DNA. Column 1, lines 27-32 indicate that the nucleic populations in the method described can be digested only with restriction enzymes that produce protruding 3'-ends because this kind of end provides protection against Exo III digestion which is used later in the process. Hence, as described in relation to *Weisman '112 '825*, both homohybrids and heterohybrids have protruding 3'-ends. Consequently, a selective elimination of homohybrids based on the ends is not possible by the method described in *Weisman '112*. Further, column 1, lines 41-55 of *Weisman '112* mention homohybrids, which are either fully methylated or non-methylated and are cleaved by restriction endonucleases that

are specific to GATC sites and sensible to methylation. The heterohybrids mentioned in column 1, lines 41-55 that have a mismatch are nicked by MutSLH. Then, all molecules are submitted to digestion by Exo III, which can initiate digestion at a nick, a blunt end or a recessed 3'-end. In this method shown in *Weisman '112*, Exo III digests cut homohybrids and nicked heterohybrids having a mismatch in the same step. Finally, the method of *Weisman '112*, leads to forked homohybrids and linear heterohybrids. This is also the opposite result of the claimed method, and as a result, *Weisman '112* does not teach or suggest the particular species of blunt ended homoduplexes and forked end heteroduplexes that are described in the claimed method.

Based on the foregoing, Applicant respectfully submits that *Weisman '112* does not teach the elimination of blunt ended homoduplexes from forked end heteroduplexes through digestion by Exo III. *Weisman '112* also does not teach selective digestion of homoduplexes versus heteroduplexes based on the ends because as shown in *Weisman '112*, these molecules are digested due to a previously made cut or nick created by a restriction enzyme or MutSLH. Thus, *Weisman '112* does not teach each and every element of the claimed invention identically and as a result does not anticipate the claims of the present application. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 23-29 and 34-45 under 35 U.S.C. § 102(e).

CONCLUSION

Applicant has properly and fully addressed each of the Examiner's grounds for rejection. Applicant submits that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 50-1067. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should be charged to undersigned's deposit account.

Respectfully submitted,

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